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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/086,217	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-98,100 and 101* is/are pending in the application.

4a) Of the above claim(s) *90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-89,91-98,100 and 101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 5/18/05, is acknowledged.

2. Claims 86-98 and 100-101 are pending.

3. Claim 90 stands withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 86-89, 91-98, 100 and 101 are under consideration in the instant application as they read on a method of treating multiple myeloma with a composition comprising an anti-VLA-4 antibody and the species of chemotherapeutic agent melphalan.

5. Applicant's IDS, filed 5/18/05, is acknowledged,

6. In view of the amendment filed on 5/18/05, only the following rejections are remained.

7. Claims 93-95 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 93-95 are indefinite in the recitation "than not administered in combination with said second composition. Claims 93-95 depend from claims 87-90 which claim the combination of both antagonist and a second composition, it is unclear how the antagonist would be administered in the absent of the second composition since the base claims require a combination therapy.

Applicant contends that claims 93-95 merely recite the dosages of the compositions, when administered in combination, relative to dosages of the compositions when administered individually. The amount of the antibody or the chemotherapeutic agent is less than would be given if one of were treated with the antibody or chemotherapeutic agent alone.

However, the issue is the lack of sufficient antecedent basis in base claims 87-90, wherein the claims require that the antibody be administered in conjunction with the chemotherapeutic agent. Base claims 87-90 do not specifically point out whether the combination therapy occurs separately, simultaneously or subsequently.

8. In view of Applicant disclosure of B epitope in the international application PCT/US99/21170 (Published as WO 00/15247), the filing date for the limitation B epitope is deemed to be the filing date of the PCT/US99/21170 application (i.e., 09/13/1999).

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 86-89, 91, 93-97 and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969) for the same reasons set forth in the previous Office Action mailed 11/16/04.

Applicant's arguments, filed 5/18/05, have been fully considered, but have not been found convincing.

Applicant submits that VanZaanen teaches the use of an anti-IL6 antibody in the treatment of MM. Masellis-smith and Lokhorst teach the use of anti-VLA-4 antibodies to treat MM. Applicant argues that none of these references teaches or suggests the use of an anti-VLA-4 antibody in combination with a chemotherapeutic agent, much less the specific combinations (e.g., anti-anti-VLA4 antibody with melphalan) in the treatment of MM. Cabot teaches the use of Melphan to treat MM. Alexanian teaches the use of melphalan in combination with prednisone (a non-biologic, non-antibody drug) to teat MM. Applicant argues that neither Cabot nor Alexanian, alone or in combination, teaches or suggests the use of a chemotherapeutic agent, e.g., melphalan, in combination with an anti-VLA-4 antibody to treat MM.

In response to Applicant's arguments that neither Smith nor Lokhorst teaches or suggest the use of anti-VLA-4 antibodies to treat MM. The Examiner notes Van Zaanen teaches an in vivo method for treating multiple myeloma comprising administering chimaeric monoclonal anti-IL-6 antibodies (cMab) in multiple myeloma patients. Further Masellis-Smith *et al* teach that the alpha4beta7 ligand is mediated MM blood B cell adhesion. Lokhorst teach monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Given the suggestions that antibodies against alpha4 integrin inhibit the adhesion of alpha4beta7 integrin of B cells from MM patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM taught by smith and that the antibodies to VLA-4 inhibited the

induced IL-6 secreation. Furthermore, Lokhorst *et al* teach that the intimate cell-cell contact is a prerequisite for IL-6 induction and the physical separation of plasma cells and LTBMC by mechanical means such as monoclonal antibodies to VLA-4 which is involved in the adhesion process, inhibit the induction of IL-6 production by LTBMC as taught by Lokhorst et al, one of ordinary skill in the art at the time the invention was made would have been motivated to subsitute the anti-IL-6 antibodies with anti-α4 antibodies in a method of treating MM and further combind the treatment with a chemotherapeutic agent such as melphalan as taugh by Cabot and Alexanian.

Applicant submits that there is no suggest or motivation in the art argued by the Examiner to combine an anti-VLA-4 antibody with a chemotherapeutic agent to treat MM, and much less the specific combination, e.g., an anti-VLA-4 antibody and melphalan. Although Alexanian teaches the treatment of MM using a combination of melphalan and prednisone (a steroid), Alexanian does not teach or suggest the use of an anti-VLA-4 antibody (a biologic) in combination with a chemotherapeutic agent. Steroids and anti-VLA-4 antibody are completely different agents, and Alexanian does not provide any teaching or suggestion to one of skill in the art to substitute an anti-VLA-4 antibody for the steroid (prenisone) disclosed in Alexanian. Applicant concluded that the Examiner has not made out a prima facie case for obviousness.

However, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07. Further, as stated in the previous office action that it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

11. Claim 92 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969). as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of Owens et al (1994) for the same reasons set forth in the previous Office Action mailed 11/16/04.

12. Claim 98 and 100 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Van Zaanen et al (Br. J. Haematol. 102:783-90, August 1998) in view of Masellis-Smith et al (IDS Ref No. A1 and Lokhorst et al (Blood 84:2269-2277, 1994) and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969), as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of U.S. Pat. No. 5,840,299 for the same reasons set forth in the previous Office Action mailed 11/16/04.

Applicant's arguments, filed 5/18/05, have been fully considered, but have not been found convincing.

Applicant argues that Van Zaanen, Masellis-Smith, Lokhorst, Cabot and Alexanian do not teach or suggest the invention as claimed, and neither Owens nor Bendig makes up for the deficiencies of the cited references.

The Examiner's response is the same as above.

Applicant has advanced the argument of unexpected results in support of non-obviousness. Applicant submits that even if a prima facie case of obviousness for these claims had been made, Applicants' surprising results would rebut the prima facie case. The claims are directed to the use of anti-VLA-4 antibodies in combination with a chemotherapeutic agent. When a combination of distinct treatments is administered to a patient, the combination cannot be expected necessarily to improve the results of either treatment alone. One can see a number of outcomes. For example, two therapeutic agents may act on the same target, such that the two agents compete with each other to modulate the same pathway. The two agents may interact with each other, for example, to form inactive heterodimers. One agent may positively modulate a favorable pathway whicle the second agent may positively modulate an undesired pathway, leading to antagonistic effects. These are only a few examples of possibilities. Given the number of possible outcomes, however, one cannot predict a priori whether a combination ot two treatmens will be beneficial or synergistic. However, Applicants have demonstrated that the combination of an anti-VLA-4 antibody and a chemotherapeutic agent produced surprisingly effective results in animal models of MM, compared to treatment with the antibody or chemotherapeutic agent alone. Applicant directs the Examiner's attention to page 72, lines 6-18 and Figure 8. Applicant note that IgG2b is indicative of tumor burden. As the graph demonstrates, treatment with the antibody alone reduced IgG2b levels, and treatment with melphalan alone reduced IgG2b levels. However, Treamen with the combination of antibody and melphalan resulted in a much more significant decrease in IgG2b levels. The result seen with the combination are much more than simply an additive effect of treatments with the antibody and melphalan alone. In fact these results demonstrate that treatment with the antibody and melphalan in combination are synergistic, compared to treatment with either agent alone. Applicant further submits that one of skill in the art would not have predicted, at the time of filing, that an anti-VLA-4 antibody and melphalan would be beneficial in combination, much less synergistic. Applicant concludes that method of combination therapy produces surprisingly effective results over antibody monotherapy or melphalan monotherapy. Applicant contends that given the surprising results achieved with Applicants' claimed methods, any potential prima facie case of obviousness has been overcome.

Applicant's reliance on unexpected superior results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997). The issue is whether the properties differ to such an extent that the difference is really unexpected. Given the teachings of the Van Zaanen et al teach a method for treating multiple myeloma comprising administering chimaeric monoclonal anti-IL-6 antibodies (cMab) in multiple myeloma patients (see the entire document and the abstract on page 783 in

particular). Further, given the teachings of the `786 patent teaches that available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug (see col., 29 under Melphalan in particular). Importantly, Alexanian et al teach a method of treating multiple myeloma using a combination therapy with melphalan and perdnisone with a higher response rate in comparison with melphalan alone (see abstract in particular). Therefore, one of ordinary skill in the art at the time of the invention was made would expect the combination therapy of anti-VLA-4 antibodies and melphalan of the invention to possess the expected beneficial result would have been produced by their combination.

Furthermore, the Examiner would like to draw Applicant's attention to U.S. Patent No. 6,692,742 who describe the same claimed unexpected surprising results. The `742 patent has found that the combination of a nitrogen mustard anticancer agent (such as melphalan), a conventionally known anticancer agent, and anti-IL-6 receptor antibody has a synergistic effect, i.e. it is more effective than the sole use of the nitrogen mustard anticancer agent or the sole use of anti-IL-6 receptor antibody for treatment of myeloma (see col. 1, line 66 to col., 2, line 6, Fig. 9 and Examples 1 and 2 in particular). Clearly the described unexpected surprising results are taught in the prior art. Therefore, one of skilled in the art at the time the invention was made would have been motivated to combine the anti-VLA-4 antibodies with the melphalan in a method of treating MM to obtain the expected beneficial results.

13. Claims 86-89, 91, 93-97 and 101 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata et al and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969) for the same reasons set forth in the previous Office Action mailed 11/16/04.

Applicant's arguments, filed 5/18/05, have been fully considered, but have not been found convincing.

Applicant submits that the `525 patent discloses the use of a small molecule VLA-4 inhibitor (oMePUPA-v) to treat animal models of pulmonary inflammation and delayed type hypersensitivity. Lee suggests that the small molecule inhibitor could also be used to treat "VLA-4 mediated cell adhesion and pathologies associated with that adhesion, such as inflammation and immune reactions" and lists 20 specific disorders within that class. Kamat discloses various anti-VLA-4 antibodies but does not teach or suggest the use of anti-VLA-4 antibodies for the treatment of MM. Further, neither Lee not Kamata teaches or suggests the use of an anti-VLA-4 antibody in combination with a chemotherapeutic agent in the treatment of MM. Cabot teaches the use of melphalan to treat MM. Alexanian teaches the use of melphalan in combination with prednisone to treat MM. Neither Cabot nor Alexanian, alone or in combination, teaches or suggests the use of a chemotherapeutic agent, e.g., melphalan, in combination with an anti-VLA-4 antibody to treat MM, as recited in the claims.

However, the `525 patent teaches a method for treating multiple myeloma in a mammal comprising administering to a compounds which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V (see patented claim 9, col., 30, and col., 4, line 21-40 in particular). The `525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo (see col., lines 57-58 in particular). Additionally, the `525 patent teaches that the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. These compounds are useful for inhibition, prevention and suppression of VLA-4-mediated cell adhesion and pathologies associated with that adhesion such as multiple myeloma (col., 2, line 64 through col., 3, line 21 in particular). Finally, the `525 patent teaches the composition is employed in dosage range from about 0.001-25 mg/kg (see col., 10, lines 60-63 in particular). Kamata et al teach that the anti-alpha 4 functional blocking antibodies such as P4C2 (epitope B2) and P4G9 (within residues 1-52) (see abstract in particular). The '786 patent teaches that melphalan is available in tablet form for oral administration and has been used to treat multiple myeloma. Further, the `786 patent teaches that available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug (see col., 29 under Melphalan in particular). Alexanian et al teach a method of treating multiple myeloma using a combination therapy with melphalan and perdnisone melphalan with a higher response rate in comparison with melphalan alone (see abstract in particular). Given that the anti-alpha-4 antibodies are functional blocking antibodies that binds to B2 epitope and that the combination therapy of MM leads to a higher response rate, one of ordinary skill in the art at the time the invention was made would have been motivated to do so because the `525 suggested the substitution implicitly because the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin such is antibodies to VLA-4. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. Further, the Kamata's et al antibodies are functional blocking. Further, melphalan is currently used in the treatment of multiple myeloma and available evidence suggests that about one third to one half of the patients with multiple myeloma show a favorable response to oral administration of the drug as taught by the `786 patent. Moreover, the motivation to combine the anti-α4 antibody with melphalan can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose (i.e., treating MM). Section MPEP 2144.07. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Applicant submits that oMePUPA-V is simply not interchangeable with anti-α4 integrin antibodies. Although Lee teaches that oMePUPA-V has a broad range of therapeutic applicability, there is simply no indication in Lee or in any other reference cited that an antibody inhibitor of α4 integrins, as recited in the claims (rather than a small molecule inhibitor), would

have the same applicability for teating MM. Applicant argues that the skilled artisan would simply not be motivated to substitute an antibody disclosed in Kamata for the small molecule drug of Lee to treat MM. Further, applicant argues that antibodies are completely different than small molecules. First, antibodies as a class of agent are vastly different in size than small molecule drugs such as oMePUPA-V. Due to its small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where it may act as either and agonist or an antagonist. In contrast, antibodies are large molecules that, although they bind to a particular epitope, effectively cover a large surface area and thereby act to block a biological pathway though stearic hindrance, as opposed to binding a specific active site or pocket. Applicant concludes that the skilled practitioner would nto have believed oMePUPA-V to be interchangeable with an anti-VLA-4 antibody to treat MM in the claimed combination methods. Second, applicant argues that an antibody-based therapy would be expected to implicate aspects of the immune response in its effect. The binding of Fc receptor by the Fc domain of an antibody molecule provides signals that activate and recruit immune and inflammatory cells, or alternatively, that send inhibitory signals that downregulate immunity. Applicant contends that the implication of additional immune mechanisms with an antibody could result in a completely different effect in vivo and that of oMePUPA-V. Applicant concludes that the skilled artisan would not have reasonably predicted that an anti-VLA-4 antibody would have the same effect as oMePUP-V in vivo in treating MM. Third, Applicant submits that anti-VLA-4 antibodies have a different specificity than oMePUPA-V. Lee teaches that oMePUP-V is highly specific for VLA-4 but does not act on $\alpha4\beta7$ integrin. Applicant points that the anti-VLA-4 antibodies recited in the claims can bind both $\alpha4\beta1/\beta7$, implicating an additional integrin pathway. Applicant contends that the broader specificity of an anti-$\alpha4$ integrin compared to oMePUPA-V, would have made it unpredictable that an anti-$\alpha4$ antibody would have the same effect as oMePUP-V in treating MM. Forth, Applicant notes that Lee discloses experiments that use oMePUPA-V to treat animal models of Pulmonary inflammation and delayed type hypersensitivity. Lee lists a broad range of other immune and inflammatory diseases that can be teated with oMePUP-V and also lists MM and tumor metastasis. Applicant contends that MM is a type of cancer that develps in a subset of white blood cells but it is nto an immune or inflammatory disorder per se, unlike the other disorders listed in Lee or the the disorders teated in the in vivo examples in Lee. There is absolutely no motivivation to select MM from this long list in Lee to treat with an antibody. Applicant contends that a skilled artisan would certainly not be motivated to use an antibody therapeutic to treat a neoplasm based on Lee's data showing that a small molecule drug against a target can be used to treat a disorder related to inflammation, or more particularly, to a hypersensitivity-type inflammation response. Applicant contends that treating neoplasms with antibodies is a completely different area of medicine than treating immune-or inflammatory-mediated diseases with small molecule drugs. Finally, Applicant argues that Lee specifically teaches that an anti-VLA-4 antibody and oMePUP-V are nto interchangeable to treat inflammatory-mediated diseases. Applicant point to Example 3 in Lee, wherein Lee compared the use of an anti-VLA-4 antibody to the use of oMePUPA-V to treat animal models of delayed type hypersensitivity. Applicant contends that the antibody was effective, but the small molecule was not. Applicant concludes that Lee does not teach or suggest the use of an anti-VLA-4 antibody in place of the small molecule oMePUP-V. Applicant further concludes that the skilled artisan would find no motivation in the combination of the cited reference to use an anti-VLA-4

antibody to treat MM. Further, Applicant submits that there is no suggestion or motivation in the cited references to combine an anti-VLA-4 antibody with a chemotherapeutic agent to treat MM.

In response to applicant's argument that a small molecule is not simply interchangeable with anti-α4 antibody, the Examiner notes that the `525 patent teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo. Further, the `525 patent administered the anti-VLA-4 antibody (PS/2) in activity in models of delayed type hypersensitivity. Further, the `525 patent teaches that the anti-VLA-4 antibody PS/2 inhibited swelling by approximately 30% whereas oMePUPA-V administered enterally was without effect in this model (see col., 22 lines 28-52, under example 3 in particular). Therefore, the `525 patent teaches anti-VLA-4 antibody that inhibited swelling in vivo which mimic the function of oMePUPA-V. Therefore, the ordinary skilled artisan would simply be motivated to substitute an antibody disclosed in Kamata for the small molecule drug.

In response to Applicant's 1st issue, the Examiner realizes that difference between the antibodies and the small molecule drugs mechanism of action, however, the issue is the obviousness for one ordinary skill in the art at the time of the invention was made to use the VLA-4 inhibitor to treat MM. The `525 patent provides a method for treating multiple myeloma in a mammal comprising administering to a compounds which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V. Additionally, the `525 patent teaches that the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. The `525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo. Therefore, the `525 suggested that suggests that anti-VLA-4 monoclonal antibodies agonists that mimic small molecule drugs can also be effective therapeutics. Furthermore, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousnes. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See MPEP 2143.02.

In response to Applicant's 2nd issue, the Examiner notes that pending claims recite antigen-binding fragments that do not require the Fc domain.

In response to Applicant's 3rd issue, first the Examiner notes that the claims uses anti-VLA-4 antibodies i.e., α4β1. Contrary to Applicant assertion that VLA-4 encompasses both α4β1 and α4β7, VLA-4 encompasses only α4β1 (see specification on page 24, lines 3-4). As such the anti-VLA-4 antibody does not have a broader specificity than the oMePUPA-V. Therefore, the anti-α4 antibody would have the same effect as oMePUP-V.

Regarding Applicant's 4th issue, the examiner notes that by statute, a U.S. patent is presumed to be valid. And claims are presumed enabled. Regarding the motivation, Applicant argues that

there is absolutely no motivation to select MM from this long list in Lee to treat with an antibody. Again, the `525 patent teaches and claims method of treating MM (see claim 9, in particular). Given the teachings of the `525 patent that the small molecule and anti-VLA-4 antibodies are capable of inhibiting VLA-4 mediated cell adhesion, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute oMEPUPA-V with anti-VLA-4 antibodies.

Regarding the 5th issue, the Examiner's position is that the `525 patent (Lee) claims are drawn to a method of treating MM with the small organic molecule, even thought the samll organic molecule has no efficacy in the delayed type hypersensitivity model. The antibody would always work, irrespective of whether the small organic molecule inhibits the delayed type hypersensitivity or not.

14. Claim 92 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata et al and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969) as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of Owens et al (1994) for the same reasons set forth in the previous Office Action mailed 11/16/04.

15. Claim 98-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view of Kamata et al and U.S. Patent No. 5,885,786 or Alexanian et al (JAM, 208:1680-1685, 1969) as applied to claims 86-89, 91, 93-97 and 101 above, and further in view of U.S. Pat. No. 5,840,299 for the same reasons set forth in the previous Office Action mailed 11/16/04.

Applicant's arguments, filed 5/18/05, have been fully considered, but have not been found convincing.

Applicant refers to the same arguments above, the Examiner's position is the same as discussed above.

Further applicant refers to the unexpected or surprising results above, the Examiner's position is the same as discussed, supra.

16. The rejection under Judicially created doctrine of Obviousness-type double patenting is hereby withdrawn because copending Application No. 09/943,659 is abandoned.

17. No claim is allowed.

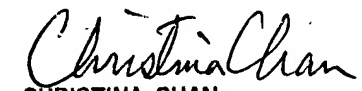
18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
July 27, 2005



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